I. THE PREPARATION OF VARIOUS 4-QUINOLINOLS

II. SOME ANALOGS OF PAMAQUINE

III. THE PREPARATION OF UNSYMMETRICAL DECAMETHYLENEDIAMINES

BY

HARRY FRED HERBRANDSON

B. Chem., University of Minnesota, 1942

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
IN THE GRADUATE SCHOOL OF THE
UNIVERSITY OF ILLINOIS, 1945

URBANA, ILLINOIS

1945

I. THE PREPARATION OF VARIOUS 4-QUINOLINOLS

II. SOME ANALOGS OF PAMAQUINE

III. THE PREPARATION OF UNSYMMETRICAL DECAMETHYLENEDIAMINES

BY

HARRY FRED HERBRANDSON

B. Chem., University of Minnesota, 1942

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
IN THE GRADUATE SCHOOL OF THE
UNIVERSITY OF ILLINOIS, 1945

URBANA, ILLINOIS

1945

ACKNOWLEDGMENT

The author would like to express his thanks to Professor C. C. Price for the direction and interest he has given to this research.

To Dr. N. J. Leonard much is due for the assistance and encouragement he has offered in the course of these studies.

R. UNIV.
BIBLIOTHEEK
LEIDEN

I. THE PREPARATION OF VARIOUS 4-QUINOLINOLS

Introduction

An economical and convenient synthesis of 7-chloro-4-quinolinol became a necessity after it was found that 4-aminoquinolines, particularly 7-chloro-4-(4-diethylamino-1-methylbutylamino)quinoline, were of considerable value in the treatment of human malaria. Price and Roberts[1] developed a synthesis of 7-chloro-4-quinolinol, and this work was undertaken as an expansion of their study.

At I. G. Farbenwerk in Elberfeld, Germany, a systematic study was made of 2,3-dialkyl-4-quinolinols as antimalarials.[2] Since, of the 142 compounds investigated, 3-*n*-heptyl-7-methoxy-2-methyl-4-quinolinol appeared to be of greatest interest, the synthesis of this compound was undertaken for the Survey of Antimalarial Drugs of the National Research Council.

Discussion

Ethyl β-*m*-chloroanilino-α-cyanoacrylate was obtained by the condensation of ethyl ethoxymethylenecyanoacetate with *m*-chloroaniline. Thermal cyclization of the acrylate yielded 7-chloro-3-cyano-4-quinolinol which was hydrolyzed to 7-chloro-4-hydroxy-3-quinolinecarboxylic acid. An alternate route to this acid was obtained by condensing N,N'-di-(*m*-chlorophenyl)formamidine with malonic ester to yield α-carbethoxy-β-*m*-(chloroanilino)acrylo-*m*-chloroanilide. This was cyclized to 7-chloro-4-hydroxy-3-quinolinecarboxy-*m*-chloroanilide which was then hydrolyzed to the acid. The 7-chloro-4-hydroxy-3-quinolinecarboxylic acid could be decarboxylated to 7-chloro-4-quinolinol as in the method of Price and Roberts.[1]

3-*n*-Heptyl-7-methoxy-2-methyl-4-quinolinol was obtained by the thermal cyclization of ethyl α-*n*-heptyl-β-*m*-methoxyanilinocrotonate. The requisite crotonate was prepared by

alkylation with heptyl iodide of ethyl β-*m*-methoxyanilinocrotonate, made from acetoacetic ester and *m*-anisidine.

BIBLIOGRAPHY

[1]Price and Roberts, private communication.

[2]Report of the Survey Office to the Panel of Review, Survey of Antimalarial Drugs, National Research Council, July 19, 1945.

II. SOME ANALOGS OF PAMAQUINE

Introduction

In an attempt to find a less toxic analog of pamaquine, 8-(4-diethylamino-1-methylbutylamino)-6-methoxyquinoline, 8-(9-diethylaminononylamino)-6-methoxyquinoline was synthesized. This compound had previously been prepared by more involved procedures.[1,2]

In anticipation of the synthesis of some drugs requiring 8-amino-6-methoxy-1,2,3,4-tetrahydroquinoline as a precursor, the preparation of this intermediate was accomplished. Balaban[3] was unable to prepare the compound by the reduction of 6-methoxy-8-aminoquinoline with tin and hydrochloric acid.

In an approach to the synthesis of the cinnoline analog of pamaquine, no successful method was found for the preparation of 8-amino-6-methoxycinnoline by ring-closure between the C_4 atom and the carbocyclic ring.

Discussion

Nonamethylene chlorohydrin, prepared from nonamethylene glycol, was treated with diethylamine to yield 9-diethylamino-1-nonanol. This was converted to the bromide hydro-

bromide which was condensed with 6-methoxy-8-aminoquinoline. The product, 8-(9-diethylaminononylamino)-6-methoxyquinoline was submitted as the dihydrobromide to the National Research Council, Survey of Antimalarial Drugs, for assay as an antimalarial.

No difficulty was experienced in the reduction of 8-amino-6-methoxyquinoline to 8-amino-6-methoxy-1,2,3,4-tetrahydroquinoline using either tin and hydrochloric acid or catalytic hydrogenation.

Thermal closure of diethyl mesoxalate 4-methoxy-2-nitrophenylhydrazone to the cinnoline was unsuccessful. Also unsuccessful were all attempted acid-catalyzed ring-closures of glyoxal phenylosazone. The 4-methoxy-2-nitrophenylhydrazone of cyanoglyoxanilide was inert to attempted cyclization with either phosphorus pentoxide or phosphorus oxychloride. With phosphorus oxychloride the imidochloride, which likewise could not be cyclized, was obtained.

BIBLIOGRAPHY

[1]Magidson, Madajewa, and Rubtsov, Arch. Pharm., **273,** 320 (1935).

[2]Altman, Rec. trav. chim., **57,** 941 (1938).

[3]Balaban, J. Chem. Soc., 2624 (1932).

III. THE PREPARATION OF UNSYMMETRICAL DECAMETHYLENEDIAMINES

Introduction

Since long-chain aliphatic diamines have amoebicidal activity,[1] several unsymmetrical decamethylenediamines were synthesized for assay as antimalarial drugs.

Discussion

Decamethylene chlorohydrin, prepared from the glycol, was caused to react with piperidine to yield the aminoalcohol. This was converted to the bromo amine hydrobromide, which on reaction with the appropriate secondary amine yielded the diamine. The dipicryl sulfonate of 10-N-piperidyl-1-(di-*n*-amylamino)decane was completely inactive on *Plasmodium lophurae* in ducklings. 10-N-Piperidyl-1-(diethylamino)decane, 10-N-piperidyl-1-(di-*n*-propylamino)decane, and 10-N-piperidyl-1-(di-*n*-butylamino)decane as the dipicryl sulfonates were sent to the National Research Council for assay against filariasis, leishmaniasis, and schistosomiasis and were found to be inactive against these infections.

BIBLIOGRAPHY

[1]British Patent 402,159; Chem. Zentr., **105** I, 2005 (1934);
British Patent 433,086; *ibid.*, **107** I, 1052 (1936);
British Patent 456,916; *ibid.*, **108** I, 4534 (1937);
U. S. Patent 2,056,867; C. A., **30,** 8241 (1936).

VITA

The writer was born in Watertown, South Dakota, on July 25, 1921. He attended the elementary schools of Watertown, South Dakota, and of Willmar, Buffalo, and Minneapolis, Minnesota, graduating from North High School, Minneapolis, in the winter of 1939. In January, 1939, he entered the University of Minnesota and received from there the Bachelor of Chemistry degree in June, 1942. That fall he entered the Graduate School of the University of Illinois as an assistant in chemistry, in which position he continued until June, 1944. Since that time he has been employed as a special research assistant on the antimalarial program of the Committee on Medical Research of the Office of Scientific Research and Development.

Digitized by the Internet Archive
in 2026

https://archive.org/details/IA41549820_0072